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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,729	ZLOKOVIC, BERISLAV V.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 27-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 27-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 1 October 2007 have been entered. Claims 7 – 26 are canceled; claims 27 – 40 are new. Claims 1 – 6 and 27 – 40 are pending and under examination.

Withdrawn Rejections

2. The following rejections set forth in the previous office action are withdrawn:

A. The rejection of claim 2 under 35 USC 102(b) as being anticipated by Shi is withdrawn in light of the amendments. Claim 1 now requires determining that inappropriate senescence is present; claim 2 requires that the patients have Alzheimer's disease. While Shi teaches determining whether patients with Alzheimer's have inappropriate senescence in endothelium, the reference teaches that they do not in fact have inappropriate senescence in endothelium. Note however the rejection of other claims over Shi is maintained as explained below.

B. The rejection under 35 USC 102(b) over Partanen is withdrawn in light of the amendments. The independent claims now all require that the patients from whom the endothelial cells are taken have a neurodegenerative disease or other cognitive impairment; the reference by Partanen teaches tissue from patients with various forms of cancer but not from patients with cognitive impairments. As the patient populations are different, the prior art reference does not anticipate the claims as currently presented.

C. The rejection under 35 USC 102(b) over Mulliken is withdrawn in light of the amendments. The independent claims now all require that the patients from whom the endothelial cells are taken have a neurodegenerative disease or other cognitive impairment; the reference by Mulliken teaches tissue from patients with various forms of cancer including hemiangioma but not from patients with cognitive impairments.

Information Disclosure Statement

3. The IDS filed 4 October 2007 has been considered. Note that the date provided by applicant for reference UR, Wikipedia entry, has been corrected. The date supplied by applicant was 1 November 2007, however that is almost one month after the IDS and the article were submitted. The examiner has corrected the date to 20 August 2007, the date of last revision of the article (see Wikipedia article, p. 3).

Rejections Maintained and Necessitated by Amendment

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, and 39 are rejected under 35 U.S.C. 102(b) as being anticpated by Shi (1996. J. Clin Invest. 98:1979 – 1990).

This rejection stands with respect to claims 1, 3, and 5 for the reasons of record and now includes new claim 39 as explained below.

Independent claims 1 and 39 each encompass determining that (claim 1) or whether (claim 39) there is inappropriate senescence in endothelium of patients with a neurodegenerative disease or another cognitive impairment. The claims are not limited to Alzheimer's patients, and do not require any particular steps. Shi teaches determining that there is inappropriate senescence in the endothelium of patients with several brain diseases, including HIV-induced neurological disease. The reference teaches that those patients with HIV-induced brain abnormalities, which are within the scope of "another cognitive impairment" recited in claims 1 and 39, have high endothelial cell apoptosis. See Shi, p. 1979, final paragraph; see also Table 1. Note particularly that the degree of apoptosis in endothelial cells of patients with severe HIV neuropathology is high, rated at 2+ or 3+ by the authors. Thus the reference anticipates claims 1 and 39. Claim 3 is rejected as the patients are human. Claim 5 is rejected as there is rejected as there is apoptosis in the endothelial cells (see Table 1).

In the remarks filed 1 October 2007, applicant argues that the reference teaches that endothelium from patients with Alzheimer's does not show altered apoptosis. The examiner agrees, hence the rejection of claim 2 was explicitly withdrawn above. However claims 1, 3, 5, and 39 encompass diseases beyond Alzheimer's, so the rejection stands.

5. Claims 1 – 3 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalaria (1997. Annals of the New York Academy of Sciences 826:263 – 271).

Kalaria teaches determining changes in endothelium from patients with Alzheimer's disease (AD) as compared to non-AD aging controls. Specifically, beginning at p. 267 final

paragraph, Kalaria teaches that immunostaining methods have been used "to define abnormalities in the cerebral endothelium and the vascular basement membrane in AD compared to aging control subjects." The reference teaches that patients with AD had "attenuation or degeneration of the endothelium in capillary profiles" (p. 268 second sentence) and "that both the length and number of degenerated microvessel profiles were significantly correlated with neocortical Aβ deposits" (p. 268 second paragraph). Thus the reference clearly teaches determining that there is "inappropriate senescence and/or defective angiogenesis in at least endothelium of the subject or cells derived" therefrom, as recited in claim 1; therefore claim 1 is anticipated.

Claim 2 is rejected as the tissue was taken from subjects with Alzheimer's disease. Claim 3 is rejected as the subjects were human. Claim 6 is rejected as there is "at least" defective differentiation of endothelial cells or inappropriate regression of capillaries, as evidenced by the improper length of capillaries and degeneration of endothelium.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 6 and 27 – 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grammas (1995. Dementia 6:126 – 130) in view of Mulliken (1982. Surgery 92(2):348 – 353, of record).

Grammas teaches that Aβ, purified from the brains of human patients diagnosed with Alzheimer's disease, inhibits the replication of endothelial cells cultured in vitro. Specifically, Grammas teaches that when Aβ from human Alzheimer's patients in contacted with rat brain endothelial cells, the rate of proliferation of those cells is decreased as compared to control-treated cells. See Grammas, p. 127 for methods of purifying Aβ from tissue and cell culture methods as well as p. 128 for the results of the experiments. As proliferation of endothelial cells derived from blood vessels is required for angiogenesis, the reference is on point to claim the "defective angiogenesis" limitation of claims 1, 27, 33, and 39. The Aβ protein was purified from human patients diagnosed with Alzheimer's disease, which is on point to claims 2 – 3, 27, 33, and 39. The endothelial cells were cultured to provide derived cells, which is on point to claims 4, 27, and 33. The cells have defective response to angiogenic signaling (i.e., the signals responsible for control of growth and proliferation of these endothelial cells; see paragraph spanning pp. 128 - 129), which is on point to claims 5, 28, and 34. However, while Grammas teaches contacting cultured rat endothelial cells with Aβ from human Alzheimer's patients, the reference does not teach culturing human endothelial cells from Alzheimer's patients and subsequently determining the degree of defective angiogenesis, as encompassed by claims 1, 4, 27, and 33.

Mulliken teaches taking tissue from human hemiangiomas and blood vessel malformations and culturing the tissue in medium. Specifically, at p. 348 Mulliken teaches obtaining the tissue surgically and the methods used to culture it. Endothelial tissue was specifically selected whereas other tissue was discarded. The reference also teaches that hemiangiomas undergo tube-formation *in vitro* and the authors report this phenomenon is *in vitro* angiogenesis (see for example p. 350, second column), which is on point to determination of defective angiogenesis as recited in claims 1, 4, 27, 33, and 39. Mulliken also reports that capillaries from human tissue can routinely be cultured *in vitro* and that these methods are suitable for determining which specific abnormalities are present in the endothelium sample. However Mulliken does not teach obtaining endothelial tissue from patients with neurodegenerative disease or another cognitive impairments as encompassed by claims 1, 27, 33, and 39.

It would have been obvious to one of ordinary skill in the art to modify the methods of Grammas to include the step of culturing the human endothelial cells, as taught by Mulliken, with a reasonable expectation of success. Specifically, it would have been obvious to one of

ordinary skill in the art to culture the tissue comprising endothelial cells from Grammas and determine the degree of defective angiogenesis. The motivation to do so would be to determine the degree of defective angiogenesis and endothelial cell proliferation in the tissue. It would be reasonable to expect success, as the reference by Grammas indicates that Aβ from human Alzheimer's patients results in defective proliferation of endothelial cells from blood vessels (i.e., angiogenesis), and the reference by Mulliken teaches how to culture endothelial cells from human tissue and teaches that this method shows the changes in endothelial cells phenotypes. Modifying the teachings of Grammas in this manner would lead to the invention set forth in claims 1 – 4, 27 – 28, 33 – 34, and 39. Claims 5 – 6, 29 – 32, 35 – 38, and 40 are included in this rejection as these claims do not require any additional method steps or starting materials, but merely recite features of the cells which are necessarily present. Note that inherent features need not be recognized at the time of invention or in the prior art (MPEP §2112(II)), and that implicit or inherent disclosures are to be considered in determinations of obviousness (MPEP § 2144.01).

Conclusion

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
December 10, 2007

RCH

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER